Randomized comparison of cold blood and cold crystalloid renal perfusion for renal protection during thoracoabdominal aortic aneurysm repair

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Objective: **More effective adjuncts are needed to reduce the incidence of acute renal injury after thoracoabdominal aortic aneurysm (TAAA) repair. The purpose of this randomized trial was to determine whether renal perfusion with cold blood provides better protection against renal ischemia than perfusion with cold crystalloid in patients undergoing TAAA repair with left heart bypass.**

Methods: **One hundred seventy-two patients were enrolled. Strict inclusion criteria were used, including planned Crawford extent II or III TAAA repair with left heart bypass. The patients were randomly assigned to receive intermittent renal perfusion with either 4°C lactated Ringer's solution (n = 86) or 4°C blood (n = 86). Renal complications within 10 days of operation were stratified by renal dysfunction score (RDS). Postoperative changes in the levels of five urinary biomarkers—retinol binding protein, α-1 microglobulin, microalbumin, N-acetyl-β-D-glucosaminidase, and intestinal alkaline phosphatase—were compared to assess potential differences in subclinical renal injury.**

Results: **Although total ischemic times were longer in the cold blood group, unprotected ischemic times were similar between the two groups. Twenty-seven patients in the cold blood group (31%) and 21 patients in the cold crystalloid group (24%) had peak RDS ≥2 (serum creatinine >50% above baseline; *P* = .4). There were no differences between the cold blood and cold crystalloid groups in the incidence of early death (7/86 [8%] vs 5/86 [6%], respectively; *P* = .8) or renal failure requiring hemodialysis (3/86 [3%] in both groups). Changes in renal biomarker levels were also similar in the two groups. Spinal cord deficits developed in 5 patients in the cold blood group (6%); there were no such deficits in the cold crystalloid group (*P* = .06).**

Conclusion: **Cold renal perfusion during TAAA repair provides effective protection against renal injury. Using cold blood instead of cold crystalloid does not enhance renal protection. (J Vasc Surg 2009;49:11-9.)**

Although many advances have been made in organ protection during thoracoabdominal aortic aneurysm (TAAA) repair, renal injury continues to be a major complication of this operation and a chief contributor to postoperative morbidity and mortality.[1-5] Several techniques have been tried in an attempt to decrease renal complications, including various methods of renal perfusion.[6-9] Our previous randomized clinical trial[10] compared two renal perfusates: cold crystalloid fluid (lactated Ringer's solution) and isothermic blood from the left heart bypass (LHB) circuit. The results showed that patients who received intermittent cold crystalloid perfusion had a significantly lower incidence of renal dysfunction than patients who received continuous isothermic blood perfusion. We concluded that the benefits of cold-crystalloid-induced renal hypothermia—including decreased metabolic demand and reduced ischemic tissue damage—outweighed the benefits of providing oxygen, nutrients, and buffers to the kidneys via isothermic blood perfusion. We then reasoned that combining these two modalities, ie, perfusing the kidneys with cold blood instead of cold crystalloid, could capitalize on their respective advantages and provide superior renal protection. Therefore, we conducted a randomized trial to determine whether perfusion with cold blood is more effective than perfusion with cold crystalloid in preventing renal complications in patients undergoing TAAA repair.

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Competition of interest: none.

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METHODS

Study design. The primary study question was whether patients who receive cold blood perfusion have a lower incidence of postoperative renal dysfunction than patients who receive cold crystalloid. Postoperative renal function was evaluated by using the renal dysfunction score (RDS), as defined by Kashyap et al[4] and used in our previous study.[10] To determine the study sample size, a power analysis was performed that was based on two assumptions derived from our previous trial:[10] first, that 21% of patients in the cold crystalloid group would develop peak RDS ≥2; and second, that, if effective, the use of cold blood would reduce the incidence of renal dysfunction by two-thirds. From these assumptions, we determined that approximately 86 patients would be needed in each group to achieve 80% power with α = .05.

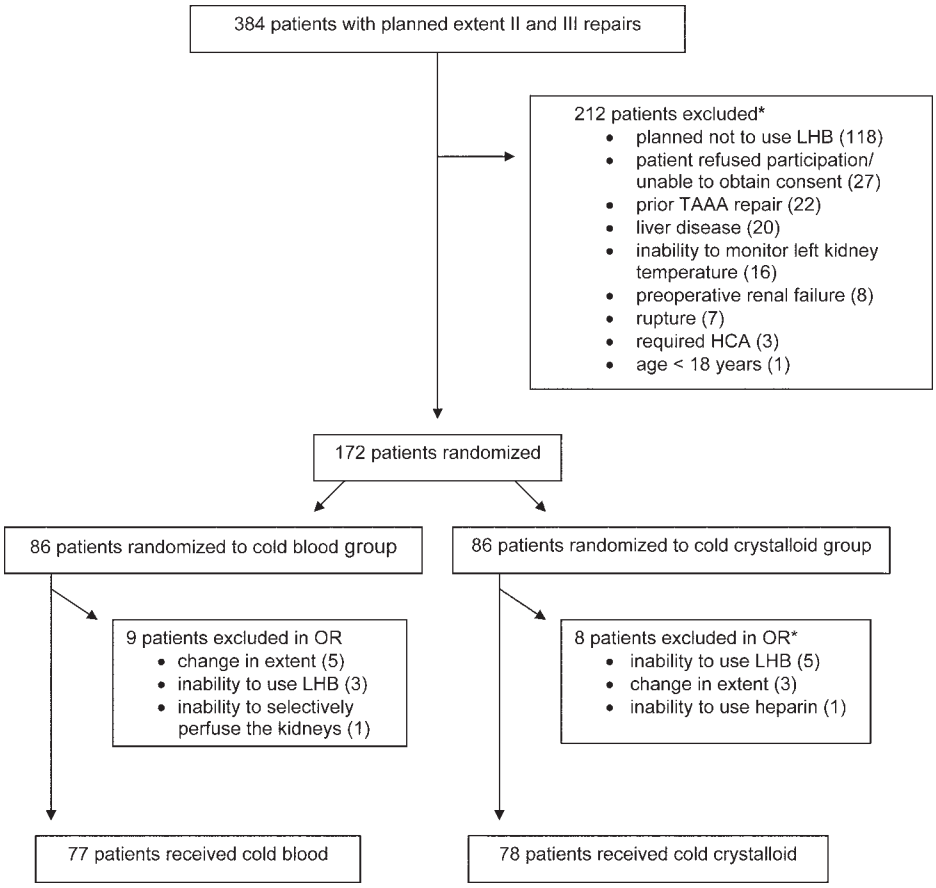

Fig 1. Flow of study patients. *HCA,* hypothermic circulatory arrest; *LHB,* left heart bypass; *OR,* operating room; *TAAA,* thoracoabdominal aortic aneurysm. *Some patients met more than one exclusion criterion.

The study was approved by the Baylor College of Medicine Institutional Review Board, and written informed consent was obtained from all enrolled patients. From Jan 2002 to Dec 2006, all patients requiring surgical repair of TAAAs were evaluated for entry into the study. The study group was limited to patients in whom Crawford extent II or III TAAA repairs using LHB were planned.[11] (We use LHB routinely in extent II repairs, but only very selectively in extent III repairs.) Preoperative exclusion criteria included planned extent I or IV repairs, planned repair without LHB, need for hypothermic circulatory arrest (HCA), prior TAAA repair, pseudoaneurysm, free aortic aneurysm rupture, inability to monitor left kidney temperature, impaired renal function (defined as renal failure requiring dialysis or serum creatinine ≥3 mg/dL), impaired left ventricular function (defined as ejection fraction <20%), liver disease (defined as conjugated bilirubin >0.3 mg/dL), age younger than 18 years, and inability to obtain consent. Blocked randomization was used to assign enrolled patients to receive either cold crystalloid or cold blood renal perfusion; patients were assigned in a 1:1 ratio and in blocks of 20. The surgical team was not blinded to the treatment assignment. All enrolled patients were blinded to the assigned perfusion strategy and were included in the intent-to-treat analysis. Intraoperative exclusion criteria applied after randomization included change in the extent of aortic replacement to descending thoracic or extent I or IV TAAA repair; LHB not being used; inability to use heparin; and inability to selectively perfuse the kidneys. Because post-randomization exclusion could introduce bias, randomized patients who received their assigned treatment were included in a separate efficacy analysis.

Patients. During the study period, TAAA repairs were planned in 738 patients, of whom 384 (52%) were to undergo extent II or III repairs (Fig 1). Two hundred twelve of these patients were excluded from enrollment because the planned repair was to be made without LHB (118 patients); the patient refused to participate, or staff could not otherwise obtain consent (27); the patient had prior TAAA repair (22), liver disease (20), preoperative renal failure (8), rupture (7), or age younger than 18 years (1); left kidney temperature could not be monitored because of large cysts, severe atrophy, or prior nephrectomy (16); or HCA was necessary (3). (Some patients had more than one reason for exclusion.) Thus, 172 patients met preoperative inclusion criteria and provided informed con-

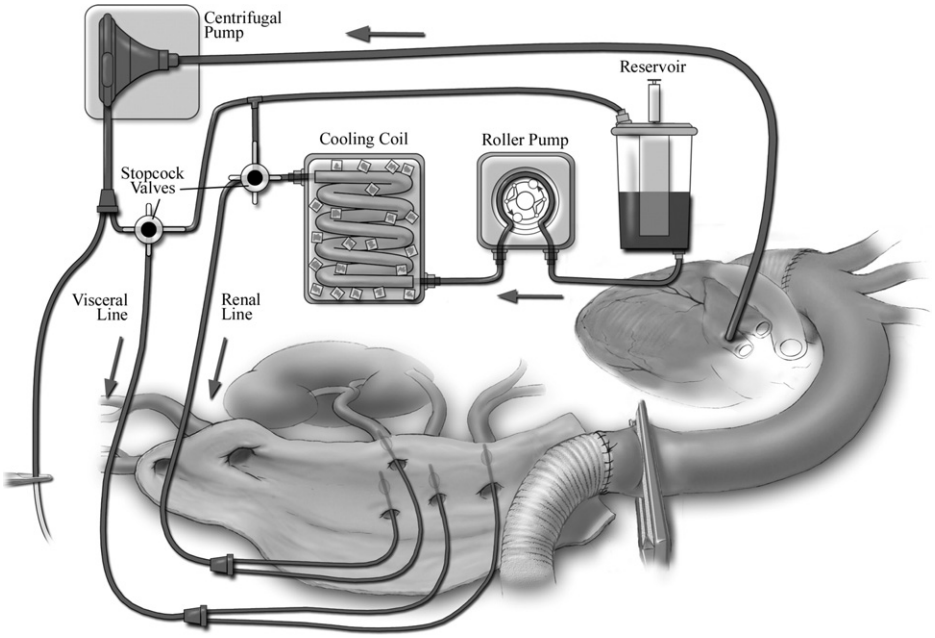

Fig 2. Diagram illustrating the circuit used for delivering cold blood renal perfusion.

sent; 86 patients (50%) were randomized to the cold blood perfusion group, and 86 patients (50%) were randomized to the cold crystalloid perfusion group. These random assignments were strictly adhered to, ie, there was no crossover between treatment groups. Seventeen randomized patients were excluded in the operating room because LHB was not used (8 patients), the extent of the repair was changed (8), the kidneys could not be selectively perfused (1), or heparin could not be used (1). Therefore, 155 patients received the assigned treatment: 77 received cold blood, and 78 received cold crystalloid.

Perfusion systems. Our standard LHB circuit included a 26F right-angled cannula (LifeStream International, Inc, The Woodlands, Tex) to drain blood via the left inferior pulmonary vein, a centrifugal pump (Biomedicus, Medtronic, Inc, Minneapolis, Minn), a return line with a 20F right-angled cannula (LifeStream International) for the distal aorta, and a second return line with two 9F Pruitt balloon perfusion catheters (Ideas for Medicine, St Petersburg, Fla) to deliver blood to the celiac and superior mesenteric arteries. The circuit did not include a heat exchanger or oxygenator.

Cold blood perfusion was delivered by a modified LHB circuit (Fig 2) that included separate visceral and renal return lines comprising Intersept Cardioplegia table lines (Medtronic Cardiopulmonary Division, Anaheim, Calif), a reservoir, a roller pump, and a cooling coil in ice. The visceral and renal return lines each terminated in two 9F Pruitt balloon perfusion catheters. The circuit was primed by gravity with 800 mL of lactated Ringer's solution, 450 mL of which was directed into the renal perfusion limb. After LHB was initiated, approximately 300 mL of blood was pumped into the renal circuit reservoir while the initial crystalloid prime was flushed out. Mannitol (1.25 g per 100 mL blood) and methylprednisolone (12.5 mg per 100 mL blood) were added to the reservoir. A recirculation line allowed continuous cooling of the blood to 4°C. The roller pump was used to deliver an initial 300 mL of cold blood to the renal arteries at a flow rate of 100 to 150 mL/minute (mean perfusion pressure was 171 ± 67 mm Hg). After each bolus infusion, the renal reservoir was refilled with blood from the circuit (along with additional mannitol and methylprednisolone) as needed to prepare for the subsequent bolus.

Cold crystalloid perfusion was delivered from a perfusion system separate from the standard LHB circuit. The circuit consisted of a cardiotomy reservoir with ¼-inch tubing going through a roller head pump. The perfusate was lactated Ringer's solution with mannitol (12.5 gm/L) and methylprednisolone (125 mg/L) cooled to 4°C. An initial bolus infusion (400-600 mL) of the solution was instilled into the renal arteries, followed by additional intermittent infusions (100-200 mL) until arterial flow was re-established.

Surgical procedure. The surgical technique used for TAAA repair in our practice has been described in detail recently.[12,13] While the necessary exposure of the thoracoabdominal aorta was obtained, the patient's body temperature was allowed to drift downward to 32°C to 34°C. A myocardial temperature probe (18-mm Mon-a-therm, Mallinckrodt Medical, Hazelwood, Miss) was inserted into the parenchyma of the left kidney. After 1 mg/kg of heparin was administered, the left pulmonary vein and supraceliac aorta were cannulated, and LHB was initiated at a flow of 500 mL/minute. The proximal and distal aortic cross-clamps were placed, and the LHB flows were increased to 2000 mL/minute. The aortic segment isolated between the two clamps was opened longitudinally, and a

woven Dacron graft was sutured end-to-end to the proximal aortic end. After the proximal anastomosis was completed, LHB was discontinued and the distal cross-clamp was removed. The remaining aneurysm was then opened longitudinally to expose the visceral arterial ostia. The celiac and superior mesenteric perfusion catheters were inserted to provide continuous perfusion with isothermic blood from the LHB circuit at an average flow rate of 400 mL/minute. The two renal perfusion catheters were placed in the renal arteries to allow intermittent perfusion with either 4°C blood or crystalloid. In patients with accessory renal arteries, only the primary artery to each kidney was perfused.

Systemic and left kidney temperatures were monitored throughout the aortic reconstruction period. The amount of cold perfusate delivered was based on a balance between achieving renal hypothermia (target left kidney temperature, <15°C; Fig 3), avoiding excessive systemic hypothermia (target body temperature, 32-34°C), and, in the crystalloid group, avoiding fluid overload (indicated by mean pulmonary artery pressure >30 mm Hg). The intercostal and visceral arteries were then reattached. The choice of technique for renal artery reattachment was based on the anatomy of the visceral vessels. In 54 patients (31%), a single patch containing the origins of all four visceral vessels was reattached to an opening in the side of the graft. One or both renal arteries were reattached separately as buttons in 60 patients (35%). Dacron interposition grafts were used to reattach one or both renal arteries in 52 patients (30%). Once the visceral arteries were reattached, the balloon perfusion catheters were removed, and the distal anastomosis was completed. The aortic clamp was removed, and protamine sulfate was given to reverse the heparin. Intravenous indigo carmine was administered, and its urinary clearance time was recorded. Diuretics were commonly administered after unclamping. Gradual, partial rewarming was facilitated by irrigating the operative field with warm saline. No patients received aprotinin.

Sample collection and analysis. Serum creatinine levels were obtained at baseline and daily on postoperative days 1 through 10. Urine samples were obtained after induction of anesthesia, after indigo carmine clearance, and on postoperative days 1, 2, 3, and 7. Five mL of urine was collected in vials containing 0.25 mL stabilizing buffer. These vials were stored at -80°C until analysis, which was completed at the University of Antwerp in Belgium. Five urinary biomarkers—retinol binding protein (RBP), α-1 microglobulin, microalbumin, N-acetyl-β-D-glucosaminidase (NAG), and intestinal alkaline phosphatase (IAP)—were evaluated. A latex immunoassay was used to analyze RBP; this involved incubating the urine samples with antibody-coated particles and measuring the agglutination with a cell counter. Both α-1 microglobulin and microalbumin markers were evaluated by using immunonephelometry (Dade Behring, Brussels, Belgium), and NAG was determined by colorimetric assay (Roche Diagnostics, Basel, Switzerland). The enzyme-antigen immunoassay was used to analyze IAP. This test was done with microtiter plates treated with anti-IAP antibody. Assay dilute was added to the wells, followed by urine samples. After incubation, the wells were rinsed, a substrate solution was added, and absorption at 405 nm was measured. All biomarkers were indexed to urinary creatinine, which was tested by the colorimetric Jaffé method and an alkaline picrate reaction to measure creatinine concentrations. All urine samples were analyzed in duplicate. For each biomarker, we determined the peak postoperative level, the difference between peak postoperative and baseline levels, and the proportion of patients in whom levels increased to 30% or more above baseline.

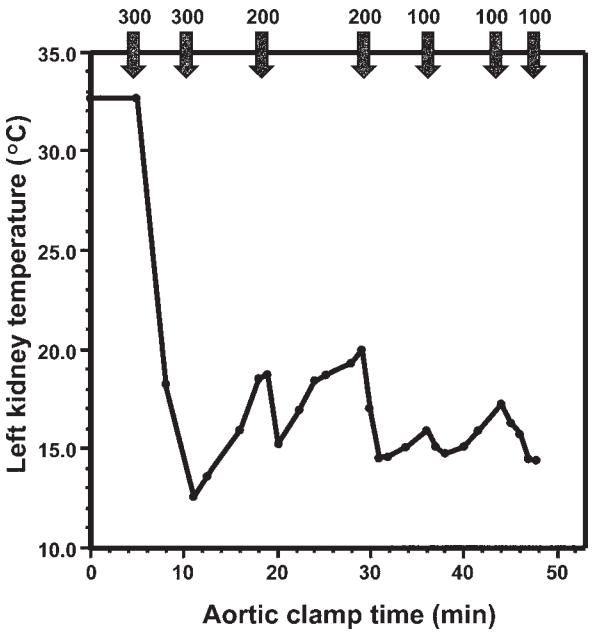

Fig 3. Representative pattern of change in left kidney temperature during intermittent cold perfusion. This patient received cold blood during an extent III thoracoabdominal aortic repair. *Arrows* indicate delivery of a cold blood bolus to both renal arteries; the volume infused is indicated above each arrow. Seven boluses (100-300 mL each) were given, providing a total renal perfusion volume of 1300 mL. The initial left kidney temperature was 32.6°C. After perfusion, kidney temperature ranged from 12.5°C to 20.0°C.

Statistical analysis. Categorical variables were analyzed with two-tailed Fisher exact tests and reported as number (and proportion) of patients. Continuous variables were presented as mean ± standard deviation; those with normal distributions were analyzed with *t* tests, whereas variables with skewed distributions were analyzed with Wilcoxon rank-sum tests. All statistical analyses were performed with the SPSS 15.0 software package (SPSS Inc, Chicago, Ill).

RESULTS

The two groups were very similar with regard to demographics and baseline laboratory and urinary marker values (Table I). The cold blood group had a higher proportion of patients with preoperative serum creatinine levels >1.5 mg/dL than the cold crystalloid group (20% vs 9%), but this difference did not reach statistical significance (P =

Table I. Comparison of preoperative characteristics

Preoperative variables	*Overall group (n = 172)*	*Blood (n = 86)*	*Crystalloid (n = 86)*	P *value*
Age (years)	62.5 ± 12.8	60.7 ± 13.6	64.2 ± 11.7	.07
Male gender	106 (62%)	56 (65%)	50 (58%)	.6
Ideal body weight (kg)[a]	77.6 ± 27.0	79.3 ± 32.2	76.0 ± 20.8	.2
Hypertension	147 (85%)	74 (86%)	73 (85%)	1.0
Diabetes	14 (8%)	6 (7%)	8 (9%)	.8
Smoking history (past or current)	137 (80%)	64 (74%)	73 (85%)	.4
Peptic ulcer disease	15 (9%)	8 (9%)	8 (9%)	1.0
Intravenous contrast (within 48 hrs)	18 (10%)	10 (12%)	8 (9%)	.8
Acetylcysteine	7 (4%)	5 (6%)	2 (2%)	.5
Aortic dissection				
Acute dissection	2 (1%)	1 (1%)	1 (1%)	1.0
Subacute dissection	6 (3%)	4 (5%)	2 (2%)	.7
Chronic dissection	71 (41%)	39 (45%)	32 (37%)	.4
Acute and chronic dissections	2 (1%)	0	2 (2%)	.5
Left renal artery occlusive disease	33 (19%)	14 (16%)	19 (22%)	.5
Right renal artery occlusive disease	34 (20%)	17 (20%)	17 (20%)	1.0
Accessory renal arteries	4 (2%)	2 (2%)	2 (2%)	1.0
Baseline serum creatinine (mg/dL)	1.1 ± 0.3	1.2 ± 0.4	1.1 ± 0.3	.1
Baseline serum creatinine ≥1.5	25 (15%)	17 (20%)	8 (9%)	.08
Creatinine clearance (mL/minute)	63.7 ± 26.3	63.7 ± 26.4	63.9 ± 26.4	1.0
Glomerular filtration rate (mL/minute/1.73m^2)[b]	67.9 ± 21.1	67.3 ± 22.5	68.6 ± 19.7	.7
Baseline urinary marker levels				
Creatinine (g)	138.2 ± 80.4	142.0 ± 76.1	134.5 ± 84.7	.5
IAP (U/g Cr)	3.6 ± 7.0	3.4 ± 6.2	3.7 ± 7.7	.8
NAG (U/g Cr)	6.6 ± 11.0	7.1 ± 11.8	6.2 ± 10.3	.6
Microalbumin (mg/g Cr)	108.4 ± 268.5	114.6 ± 266.0	102.1 ± 272.4	.8
RBP (g/g Cr)	75.3 ± 35.9	65.8 ± 27.3	84.8 ± 42.9	.7
α_1 microglobulin (mg/g Cr)	17.0 ± 43.8	14.7 ± 18.9	19.2 ± 59.1	.5

Cr, Urinary creatinine; *IAP,* intestinal alkaline phosphatase; *NAG,* N-acetyl-β-D-glucosaminidase; *RBP,* retinol binding protein.
[a]Ideal body weight was estimated as 50 kg + 2.3 kg for each inch over 5 feet for men and 45.5 kg + 2.3 kg for each inch over 5 feet for women.
[b]Glomerular filtration rate was calculated using the Modification of Diet in Renal Disease equation.[14]

.08). Most patients (92%) underwent extent II repair, and only 14 (8%) underwent extent III repair (Table II). Most repairs were elective (n = 150, 87%). There were significant differences in several total ischemic times, with the cold blood group having longer ischemia times for the intercostal arteries, the right and left legs, and the right renal artery. All unprotected ischemic times, however, were similar between groups. Although the perfusate volume fell within the desired range (600-1800 mL), we were only able to achieve intraoperative renal temperatures below 15°C in 37% of all patients. However, the two perfusion techniques were similarly effective in achieving satisfactory levels of renal hypothermia (Table III); left kidney temperature reached <20°C in 112 of the 155 patients (72%) who received cold perfusion, and deep hypothermia (defined as <28°C) was achieved in nearly all patients. Despite a mean lowest body temperature of 32.1°C, only 4 patients had intraoperative dysrhythmias (2%); all 4 had atrial fibrillation, and 1 also had transient ventricular tachycardia (at 30°C) that resolved after lidocaine administration.

The intent-to-treat analysis revealed no differences in renal outcomes between the two groups (Table IV). Twenty-seven patients in the cold blood group (31%) and 21 patients in the cold crystalloid group (24%) had peak RDS ≥2 (serum creatinine >50% above baseline; $P = .4$). Similarly, 12 patients in the cold blood group (14%) and 10 patients in the cold crystalloid group (12%) had peak RDS ≥3 (serum creatinine >100% above baseline; $P = .8$), and only 3 patients in each group (3%) had peak RDS = 5 (renal failure requiring hemodialysis). Changes in renal injury biomarker levels (relative to baseline) were also similar in the two groups (Table IV), as were the absolute peak biomarker levels and the proportion of patients who had a 30% increase in biomarker levels (data not presented). There were no differences between the cold blood and cold crystalloid groups in the incidence of early death (7/86 [8%] vs 5/86 [6%], respectively; $P = .8$). Whereas 5 patients (6%) in the cold blood group experienced postoperative paraplegia or paraparesis, no patients in the cold crystalloid group experienced this adverse event ($P = .06$). The efficacy analysis, which only included the 155 patients who received the assigned treatment, confirmed the similarities in renal outcomes in the two groups (data not presented). Among the 25 patients in the subgroup who had preoperative serum creatinine levels >1.5 mg/dL, only 2 (8%) had peak RDS ≥3; both patients were in the cold blood group (2/17 [12%] vs 0/8; $P = 1.0$).

The degree of hypothermia achieved did not affect renal outcomes. Peak RDS ≥2 occurred in 17 of the 64 patients (27%) in whom the left renal temperature target of <15°C was reached and in 31 of the 108 patients (29%) in whom the target temperature was not reached ($P = .9$). Similarly, peak RDS ≥3 occurred in 9 of the 64 patients (14%) in whom the left renal temperature reached <15°C

Table II. Comparison of intraoperative variables

Intraoperative variables	*Overall group (n = 172)*	*Blood (n = 86)*	*Crystalloid (n = 86)*	P *value*
Extent of repair[a]				
Extent II repair	158 (92%)	82 (95%)	76 (88%)	.2
Extent III repair	14 (8%)	4 (5%)	10 (12%)	.2
Renal artery reattachment technique				
Single patch	54 (31%)	27 (31%)	27 (31%)	1.0
Single separate renal attachment	46 (27%)	22 (26%)	24 (28%)	.9
Single renal interposition graft	33 (19%)	15 (17%)	18 (21%)	.7
Single beveled distal anastomosis	13 (8%)	8 (9%)	5 (6%)	.6
Bilateral renal interposition grafts	12 (7%)	7 (8%)	5 (6%)	.8
Bilateral separate renal attachments	7 (4%)	2 (2%)	5 (6%)	.4
One separate renal attachment + one renal interposition graft	7 (4%)	5 (6%)	2 (2%)	.4
Urgency of repair				
Elective	150 (87%)	75 (87%)	75 (87%)	1.0
Urgent	17 (10%)	9 (10%)	8 (9%)	1.0
Emergent	5 (3%)	2 (2%)	3 (3%)	1.0
Cerebrospinal fluid drainage	157 (91%)	81 (94%)	76 (88%)	.7
Total aortic cross-clamp time (minutes)	71.1 ± 24.4	74.4 ± 27.7	67.8 ± 20.8	.08
Total cross-clamp time >100 minutes	14 (8%)	9 (10%)	5 (6%)	.4
Left heart bypass time (minutes)	25.1 ± 10.1	25.6 ± 9.5	24.6 ± 10.8	.5
Intercostal ischemic times (minutes)				
Total ischemic time[b]	57.3 ± 14.3	60.0 ± 9.5	54.8 ± 13.7	.02
Unprotected ischemic time[c]	37.0 ± 12.1	37.9 ± 13.0	36.0 ± 11.2	.3
Celiac ischemic times (minutes)				
Selective perfusion time	19.8 ± 10.2	20.0 ± 9.2	19.5 ± 10.7	.8
Total ischemic time[b]	61.5 ± 14.9	62.6 ± 14.3	60.4 ± 15.5	.3
Unprotected ischemic time[c]	40.8 ± 11.6	40.7 ± 12.5	40.9 ± 10.8	.9
Superior mesenteric ischemic times (minutes)				
Selective perfusion time	19.7 ± 10.0	20.3 ± 9.1	19.2 ± 10.8	.5
Total ischemic time[b]	61.4 ± 14.7	62.6 ± 14.1	60.3 ± 15.3	.3
Unprotected ischemic time[c]	40.7 ± 11.5	40.7 ± 12.3	40.8 ± 10.6	.9
Right leg ischemic times (minutes)				
Total ischemic time[b]	64.6 ± 20.1	67.8 ± 23.2	61.4 ± 15.9	.04
Unprotected ischemic time[c]	43.8 ± 18.1	45.8 ± 22.7	41.9 ± 11.7	.2
Left leg ischemic times (minutes)				
Total ischemic time[b]	64.3 ± 18.7	67.2 ± 21.0	61.5 ± 15.7	.04
Unprotected ischemic time[c]	45.2 ± 25.4	48.3 ± 33.8	42.0 ± 11.6	.1
Right renal ischemic times (minutes)				
Total ischemic time[b]	61.8 ± 14.8	64.0 ± 14.6	59.5 ± 14.7	.05
Unprotected ischemic time[c]	41.1 ± 11.7	42.0 ± 12.9	40.2 ± 10.3	.3
Left renal ischemic times (minutes)				
Total ischemic time[b]	66.3 ± 20.0	68.9 ± 20.5	63.7 ± 18.4	.08
Unprotected ischemic time[c]	45.7 ± 16.8	46.8 ± 19.1	44.6 ± 14.0	.4
Total renal ischemic time > 60 minutes[b]	31 (18%)	17 (20%)	14 (16%)	.7
Left kidney temperature (°C)				
Baseline temperature[d]	33.0 ± 2.2	33.1 ± 2.4	33.0 ± 1.9	.7
Lowest temperature	16.9 ± 6.1	17.4 ± 6.8	16.5 ± 5.4	.4
Left kidney temperature < 15°C	64 (37%)	33 (38%)	31 (36%)	.9
Nasopharyngeal temperature (°C)				
Baseline temperature[d]	34.2 ± 1.0	34.2 ± 1.1	34.2 ± 1.0	.6
Lowest temperature	32.1 ± 1.2	32.2 ± 1.0	32.0 ± 1.2	.2
Last recorded temperature	32.9 ± 0.9	33.0 ± 0.8	33.0 ± 1.0	.9
Total renal perfusion time (minutes)	7.6 ± 3.1	8.2 ± 3.4	6.9 ± 2.8	.01
Total renal perfusion volume (mL)	1001.0 ± 531.3	1037.0 ± 687.6	966.1 ± 319.1	.4
Urine output during operation (mL)	1165.3 ± 775.6	1148.9 ± 808.7	1181.4 ± 746.6	.8
Urine indigo carmine clearance time (minutes)	21.4 ± 20.6	20.9 ± 16.6	22.0 ± 24.0	.7
Transfusion requirements (U)				
Packed red blood cells	3.5 ± 3.2	3.5 ± 2.5	3.4 ± 3.7	.9
Fresh frozen plasma	6.7 ± 5.5	6.7 ± 5.7	6.7 ± 5.3	1.0
Cryoprecipitate	2.5 ± 7.6	3.4 ± 8.9	1.5 ± 5.9	.1
Post-clamp diuretics administered	157 (91%)	82 (95%)	75 (87%)	.5
Intraoperative dysrhythmias	4 (2%)	1 (1%)	3 (3%)	.6

[a]The classification of TAAAs followed the schema defined by Crawford et al.[11] Extent II repairs involved graft replacement of most of the thoracoabdominal aorta, usually beginning near the left subclavian artery and extending into the infrarenal aorta. Extent III repairs only replaced the lower descending thoracic aorta (ie, below the sixth rib) and extended a variable distance into the abdominal aorta.

[b]Total ischemic time was defined as the time from aortic clamping to removal of the clamp and reinstitution of blood flow to the region.

[c]Unprotected ischemic time was defined as total ischemic time minus left heart bypass time.

[d]Baseline nasopharyngeal and left kidney temperatures were recorded before the aorta was clamped.

Table III. Effectiveness of achieving renal hypothermia

Lowest left kidney temperature	*Overall group (n = 155)*	*Blood (n = 77)*	*Crystalloid (n = 78)*	P *value*
<15°C	64 (41%)	33 (43%)	31 (40%)	.7
<20°C	112 (72%)	53 (69%)	59 (76%)	.4
<28°C	151 (97%)	75 (97%)	76 (97%)	1.0

and in 13 of the 108 patients (12%) in whom the target temperature was not reached ($P = .8$).

DISCUSSION

Previously, most strategies for renal protection during TAAA surgery employed either hypothermia or blood perfusion. The protective effects of renal hypothermia are well established.[15-17] In contrast, perfusion with isothermic blood does not seem to be as effective as hypothermia[10] and may actually increase the risk of renal injury.[18] However, perfusion with blood does offer several potential benefits, including delivery of oxygen and buffers, prevention of cell membrane damage, and reduction of intracellular swelling. Like various techniques described by other groups,[8,19-23] the use of cold blood in this randomized trial was an attempt to combine the benefits of hypothermia and blood perfusion, in the hope of further reducing the incidence of renal dysfunction. The perfusion system we investigated delivered blood to the kidneys, achieved deep renal hypothermia (<28°C), maintained acceptable systemic temperatures without active warming, and was incorporated into a standard LHB circuit. Nonetheless, our findings did not support our hypothesis that cold blood is more effective than cold crystalloid in preventing renal complications in patients undergoing TAAA repair. We acknowledge that changes in delivery technique, such as using continuous perfusion instead of intermittent perfusion, might make cold blood perfusion more effective.

Although we used a target left kidney temperature of <15°C to guide perfusion during the study, the data show that this target is frequently not reachable within the constraints of avoiding fluid overload and severe systemic hypothermia. More importantly, based on the post hoc comparison of patients who reached the 15°C target with those who did not, temperatures between 15°C and 28°C appear to be as effective as temperatures below 15°C, suggesting that it is not necessary to achieve profound renal hypothermia to provide renal protection.

Our primary outcome was based on the postoperative RDS, which quantifies the severity of renal dysfunction by comparing baseline and peak serum creatinine levels. When compared to using renal failure requiring hemodialysis as an endpoint, RDS is more sensitive in detecting postoperative renal complications, which allows a much smaller sample size. However, changes in serum creatinine occur well after renal injury has occurred, making RDS relatively insensitive in detecting renal parenchymal damage. For this reason, we used urinary biomarkers as indicators of subclinical renal injury.[24] Several studies have examined the use of urinary biomarkers to detect renal injury associated with cardiovascular operations.[25-27] The urinary markers used in the present study—RBP, α-1 microglobulin, microalbumin, NAG, and IAP—were selected because they were known to be effective in detecting renal injury when this study was initiated.[28-34] Since the start of our study, several new biomarkers—such as neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, and cysteine-rich protein 61—have surfaced[35-37] and merit consideration for evaluating renal function in future trials.

Several limitations of this study warrant discussion. First, the potential for cold blood to provide renal protection by delivering oxygen, nutrients, and buffers to the ischemic kidney is entirely theoretical. We have not studied these properties in 4°C blood, but we recognize that cold temperatures shift the oxyhemoglobin dissociation curve to the left, reducing the blood's ability to release oxygen. Nevertheless, cold blood perfusion is widely used in cardiac surgery to prevent ischemic complications, both as a component of blood cardioplegia for myocardial protection and as the perfusate used for selective antegrade cerebral perfusion during operations requiring HCA. Furthermore, several centers have used cold blood perfusion to provide renal protection.[8,19-21,23] It was this clinical precedence that stimulated us to formally compare cold blood with cold crystalloid.

Second, although the study groups were well-matched in most areas, the cold blood group had longer total ischemic times and a trend toward a higher incidence of spinal cord deficit, even though unprotected ischemic times were similar in both groups. The reason for the difference in total ischemic times is not clear, because there were no substantial differences in the frequency of aortic dissection, the extent of repair, or the urgency of operation. Nor were there significant differences in body temperature, the prevalence of diabetes, or the use of cerebrospinal fluid drainage, factors known to affect the risk of spinal cord injury.[38] Of note, our risk model for predicting paraplegia rates in groups undergoing TAAA repair estimated equivalent risks (10%) for the two groups.[39]

Third, we did not collect data related to pulmonary complications. These data would have been valuable, given that the use of cold crystalloid (vs re-infusion of the patient's cooled blood) involved infusing, on average, nearly 1 liter of fluid. Although this infusion of additional crystalloid was not associated with an increase in length of hospital stay, we cannot determine whether the increase in fluid administration translated into more pulmonary complications.

Finally, we were not able to use the recently established RIFLE classification system for acute renal injury,[40] which uses both glomerular filtration rate (GFR) criteria and urine output criteria to place patients in Risk, Injury, Failure, Loss, and End-stage kidney disease categories. Our study was designed and initiated before RIFLE became well established. Consequently, although we collected daily postoperative urine output data, we did not collect the hourly urine output data needed to determine RIFLE class. However, it is notable that if the RIFLE GFR criteria are applied to our patients, the Risk category corresponds to an

Table IV. Comparison of outcomes

Outcomes	*Overall group (n = 172)*	*Blood (n = 86)*	*Crystalloid (n = 86)*	P *value*
Peak serum creatinine (mg/dL)	1.7 ± 1.0	1.7 ± 0.9	1.7 ± 1.1	.7
Increase in urinary marker levels[a]				
Creatinine (g)	84.8 ± 73.5	82.5 ± 73.6	86.7 ± 73.9	.7
IAP (U/g Cr)	6.5 ± 17.4	8.0 ± 23.6	5.1 ± 6.8	.3
NAG (U/g Cr)	36.0 ± 214.4	52.5 ± 300.9	19.4 ± 29.3	.3
Microalbumin (mg/g Cr)	367.4 ± 1777.1	537.2 ± 2485.5	195.5 ± 283.9	.2
RBP (g/g Cr)	39.1 ± 75.7	39.3 ± 74.0	38.8 ± 77.9	1.0
α_1 microglobulin (mg/g Cr)	150.5 ± 160.9	160.6 ± 189.6	140.3 ± 125.6	.4
Postoperative dopamine infusion	140 (81%)	70 (81%)	70 (81%)	1.0
Peak RDS				
1	124 (72%)	59 (69%)	65 (76%)	.6
2	26 (15%)	15 (17%)	11 (13%)	.5
3	13 (7%)	8 (9%)	5 (6%)	.6
4	3 (2%)	1 (1%)	2 (2%)	1.0
5	6 (3%)	3 (3%)	3 (3%)	1.0
Average daily urine output (mL)	2126.6 ± 1961.9	2128.7 ± 1796.5	2124.6 ± 2121.8	1.0
Paraplegia/paraparesis	5 (3%)	5 (6%)	0	.06
Hospital length of stay (days)	15.7 ± 12.7	15.7 ± 10.3	15.7 ± 14.7	1.0
Operative mortality	12 (7%)	7 (8%)	5 (6%)	.8
In-hospital mortality	10 (6%)	6 (7%)	4 (5%)	.7
30-day mortality	10 (6%)	6 (7%)	4 (5%)	.7

Cr, urinary creatinine; *IAP,* intestinal alkaline phosphatase; *NAG,* N-acetyl-β-D-glucosaminidase; *RBP,* retinol binding protein; *RDS,* renal dysfunction score.
[a]Increases in biomarker levels were calculated as the difference between peak postoperative levels and baseline levels.

RDS of 2 (50% increase in creatinine vs baseline), and the Injury category corresponds to an RDS of 3 (doubling in creatinine vs baseline). Nevertheless, future studies of renal protection during TAAA repair would benefit by using RIFLE classification as an endpoint.

Despite these limitations, this randomized trial shows that using cold renal perfusion during TAAA repair provides effective protection against renal injury, but using cold blood instead of cold crystalloid does not enhance renal protection. In light of these results, we currently use cold crystalloid renal perfusion, which is somewhat less cumbersome than the cold blood technique. Future studies will evaluate the efficacy of combining cold crystalloid perfusion with other renal protection strategies.

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AUTHOR CONTRIBUTIONS

Conception and design: SL, LC, SR, JC
Analysis and interpretation: SL, MJ, XW, JC
Data collection: MJ, SC, LC, MC
Writing the article: SL, MJ, MC, XW, SR
Critical revision of the article: SL, MJ, SC, LC, XW, SR, JC
Final approval of the article: SL, MJ, SC, LC, MC, XW, SR, JC
Statistical analysis: SL, MJ, XW
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Overall responsibility: SL, JC

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DISCUSSION

Dr Richard Cambria (Boston, Mass). Congratulations on a well-conducted and obviously exhaustively detailed study. I think you've shown, and it's always nice to see, data that reinforces one's bias that cold crystalloid perfusion, of course, can be a very effective means of renal protection during these extensive operations. And my major question was detailed on your slide that your data showed that the renal ischemic times are really identical between the two.

Of course, we also know that the patients with baseline abnormal renal function are those that are at the highest risk for perioperative renal dysfunction. So I certainly agree with the conclusions and the tenets of your study. And although it's not the topic of this study, I wonder if you could give us your data or thoughts on cold renal protection in those with baseline renal insufficiency.

Dr Coselli. Absolutely, it was not the intent of this particular evaluation to determine whether one technique was superior over another in patients with preoperative renal dysfunction. In fact, as I showed, impaired renal function was an exclusion criterion for this specific randomized trial.

However, off the cuff (and leaning more towards opinion but somewhat away from speculation), just based on experience, we have employed cold crystalloid perfusion in patients with preoperative renal dysfunction and have found it to be quite favorable; but we haven't analyzed it in a rigorous statistical way, so it nowhere near approaches Level 1 data.